CURABLE COMPOSITIONS WITH ANTIMICROBIAL PROPERTIES

This application claims the benefit of U.S. Provisional Application No. 60/075,176 filed Feb.19, 1998, U.S. Provisional Application No. 60/075,246 filed Feb.19, 1998 and U.S. Provisional Application No. 60/094,823 filed Jul. 31, 1998 and hereby incorporates the subject matter of those applications by reference in their entireties for all purposes.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to improvements in curable compositions intended for use or placement in direct contact with a biological surface. More specifically, this invention discloses curable compositions with antimicrobial properties, together with methods for their use, which are useful for preventing microbial growth on one or more surfaces of the curable composition or within the curable composition or adjacent to the curable composition after curing and subsequent placement in contact with a biological surface.

2. Description of Related Art

Materials science has provided us with a plethora of compositions that can be transformed from an initial, malleable state to a final, non-malleable state, generally through the process of heating, the application of pressure, and/or the inducement of polymerization. Such compositions provide us with an array of materials that may be first molded into a desired shape, then subsequently induced to transform into a final, non-deformable shape identical (or nearly so) to the original molded shape. Such processes may employ heat or pressure (or both) to transform materials into a desired shape by manipulation of the physical properties of the material itself, or may alternatively utilize initiators and/or activators to begin a polymerization reaction throughout the shaped mass. Alternatively, a curing process may occur simply as a composition absorbs moisture from the surrounding environment. Such curing processes are seen in certain types of adhesives, such as urethanes-based caulks and denture adhesives.

The class of materials known as acrylics (which, for the purpose of this disclosure, shall mean compositions comprised wholly or in part of acrylate and/or methacrylate monomers and/or polymers, alone or in combination with each other and/or other unsaturated and/or saturated compounds) has gained acceptance as being particularly suited for the formation of prosthetics to be placed into contact with the body. In particular, acrylics have been used to form dental restorative materials, dentures, temporary crown and bridge materials, and artificial fingernails and toenails, as well as having been employed as adhesion promoters at the interface between a biological surface (herein defined as any external or internal surface of a living organism) and a prosthetic (in order to provide the extended wear time required of, for instance, a permanent dental restorative material). Curable acrylic compositions, when properly initiated or catalyzed, undergo free-radical addition reaction polymerization, which is exothermic (i.e. generates heats) in character.

As biological surfaces are invariably populated by a wide variety of microorganisms, inert objects (such as prosthetics or adhesives), when placed in contact with such surfaces are subject to surface colonization and, often, subsequent penetration by those same microorganisms. In addition, fluid infiltration at the interface between the biological and non-

biological surfaces presents ideal conditions for the growth of microorganisms. In the absence of any protective mechanism to prevent such colonization, objects in contact with biological surfaces often become populated with a higher density of microorganisms than the original biological surface itself. Thus a prosthetic can become a breeding ground for potentially harmful microorganisms and subsequently itself become a source of infection to adjacent living tissue. For example, the occluded interface or margin between an inert object and a biological surface, due to the accumulation of moisture there (and often, the exclusion of oxygen, which results in an environment conducive to the growth of anaerobic microorganisms), can foster the development of microbial colonies in higher numbers than the same biological surface would have in a non-occluded state.

One example of this interfacial phenomenon is recurrent caries, which is though to be caused by the infiltration of microorganisms, in particular, those responsible for dental caries (tooth decay), into the interface margin between a dental restorative material (such as an amalgam or resin-based composite) and the natural tooth surface. In the process of preparing, placing and finishing a dental restoration, the marginal adaptation of the restorative material, in addition to the quality and strength of the bond between the restoration and the natural tooth surface, is of paramount importance to the restoration's longevity as a permanent prosthetic. If the adhesion of the restorative material is inadequate, or the shape of the restorative material is slightly non-conforming, oral fluids such as saliva, which constantly bathe the restoration, are able to infiltrate into the interface between the restorative material and the natural tooth. Microorganisms are carried along with the infiltrating fluids and may colonize the marginal space. The metabolites of certain microorganisms, such as *Streptococcus mutans* species, are potentially harmful to the natural tooth structure, and erosion of the tooth at the interface (recurrent caries and possible restoration failure) may occur over time.

Recurrent caries have been shown to be a major cause in the failure of dental restorations. The failure is thought to occur due to penetration of pathogenic organisms which as *S. mutans* into the tooth structure along the cavity wall through microleakage and/or accumulation of bacteria at the margins, or interface, between the restorative material and the tooth. The incidence of recurrent caries around restorations involving enamel can be reduced by using fluoride containing restorative materials. However, the amount of fluoride released has been shown to decrease significantly with time and thus cariostatic ability of these restorative materials over a long term remains unclear. To overcome this advantge, attempts have been made to supplement restorative materials with antimicrobial agents. Addition of chlorhexidine, a water soluble catonic antimicrobial agent to composite restorative materials ahve largely been unsuccesful because of the loss of efficacy and deterioration of physical properties. Attempts have also been made to add other types of antimicrobial agents to restorative materials. Recently, Imazato, et al. U.S. Pat. No. 5,733,949 incorporated methacryloyloxydodecylpyridinium bromide (MDPB) to experimental composites and showed that the attachment of *S. mutans* to surfaces of the restorative material was reduced. However, unlike chlorhexidine, no zone of inhibition was evident by the disk diffusion method, indicating that the agent is not released oris released at sub MIC levels. This finding suggests that MDPD has a potential disadvantage becasue it does not solve the problem of permeation of bacteria through the enamel-restoration interfaces and destroying bacteria in the cavity preparation.